IN THE U TED STATES PATENT AND TRA MARK OFFICE PATENT/ APPLICATION

Re: Appeal to the Board of Patent Appeals and Interferences

GP1645

In re PATENT APPLICATION of
Inventor(s): LEE
Appln. No.: 08 (Series Code ↑) 971,338 (Serial No. ↑)
Filed: November 17, 1997
Title: GDF-1 PROTEIN

Group Art Unit: 1645
Examiner.: M. Allen
Atty. Dkt. PM 241801 (M#) (Client Ref)

OIPE JUL 03 2000 PATENT & TRADEMARK OFFICE

Date: July 3, 2000

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Asst. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

1. ☐ **NOTICE OF APPEAL**: Applicant hereby appeals to the Board of Patent Appeals and Interferences from the decision (not Advisory Action) dated November 2, 1999 of the Examiner twice/finally rejecting claim(s) in this application or in this application and its parent application.
2. ☒ **BRIEF** on appeal in this application attached in triplicate (extendable up to 5 months).
3. ☐ An **ORAL HEARING** is respectfully requested under Rule 194 (due two months after Examiner's Answer- unextendable
4. ☐ Reply Brief is attached in triplicate (due two months after Examiner's Answer – unextendable).
5. ☒ "Small entity" verified statement filed: ☐ herewith. ☒ previously.

6. FEE CALCULATION

			Large/Small Entity		Fee Code
If box 1 above is X'd, see box 12 below first and decide:		enter	$300/150*	$150	119/219
If box 2 above is X'd, see box 12 below first and decide:		enter	$300/150*	$0	120/220
If box 3 above is X'd, see box 12 below first and decide:		enter	$260/130*	$0	121/221
If box 4 above is X'd,		enter nothing	- 0 - (no fee)		
7. Original due date: April 1, 2000					
8. Petition is hereby made to extend the original due date to cover the date this response is filed for which the requisite fee is attached.	(1 mo)	$110/$55			115/215
	(2 mos)	$380/$190			116/216
	(3 mos)	$870/$435			117/217
	(4 mos)	$1360/$680			118/218
	(Usable only if box 2 is X'd— 5 mos)	$1850/$925	+435		128/228
9. Enter any previous extension fee paid ☐ previously since above original due date (item 7); ☐ with concurrently filed amendment.....			-0		
10. **Subtract line 9 from line 8 and enter: Total Extension Fee**				+435	
11.			**TOTAL FEE ATTACHED =**	$585	

12. ☐ *Fee NOT required if/since paid in prior appeal in which the Board of Patent Appeals and Interferences did not render a decision on the merits.

(Our Deposit Account No. 03-3975)
(Our Order No. 20055 (C#) 241801 (M#)

CHARGE STATEMENT: The Commissioner is hereby authorized to charge any fee specifically authorized hereafter, or any missing or insufficient fee(s) filed, or asserted to be filed, or which should have been filed herewith or concerning any paper filed hereafter, and which may be required under Rules 16-18 (missing or insufficiencies only) now or hereafter relative to this application and the resulting Official Document under Rule 20, or credit any overpayment, to our Accounting/Order Nos. shown above, for which purpose a duplicate copy of this sheet is attached. This CHARGE STATEMENT does not authorize charge of the issue fee until/unless an issue fee transmittal sheet is filed.

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NOTE: File this cover sheet in duplicate with PTO receipt (PAT-103A) and attachments

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

JUL 07 2000

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In re Patent Application of

LEE

Appln. No. 08/971,338

Filed: November 17, 1997

FOR: GDF-1 PROTEIN

Group Art Unit: 1645 #15

Examiner: M. Allen Plunkett 7/12/00

* * *

July 3, 2000

BRIEF UNDER 37 CFR § 1.191 ET SEQ.

Hon. Commissioner for Patents
Washington, D.C. 20231

Sir:

A Notice of appeal was timely filed pursuant to Rule 191(a) on February 1, 2000. This brief is now filed in triplicate to appeal the Examiner's final rejection of the pending claims. Reversal of that final rejection is respectfully requested.

A petition and fee for a three-month extension to the due date for this brief is being filed herewith. Thus, it is timely filed because July 1, 2000 was a Saturday.

(1) Real Party in Interest

By assignment recorded on January 16, 1991 starting at reel 5582/frame 0799, rights in the subject invention were assigned to the Carnegie Institution of Washington. An exclusive license was granted to Cambridge NeuroScience who has sublicensed Creative BioMolecules.

(2) Related Appeals and Interferences

The appeal of divisional U.S. Appln. No. 08/966,233 will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

(3) Status of Claims

Claims 4-10 and 22-33 are pending and stand rejected. All other claims have been canceled. The final rejection of all pending claims is appealed.

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(4) Status of Amendments

The Examiner made her rejections of claims 4-10 and 22-33 final in the Office Action of November 2, 1999. No amendment of the claims was proposed subsequent to that final rejection. Claims on appeal are set forth in the Appendix.

(5) Summary of Invention

In concise form, the invention of claims 4-10 and 22-33 is directed to the GDF-1 protein and methods of purifying GDF-1 protein.

Support for the claimed invention is shown by original claims 4-10 and page 10, line 15, to page 12, line 7 of the specification. Figure 3 shows that GDF-1 is distinguishable from other members of the TGF-β superfamily. Particular examples illustrating the claimed invention are the following: Figures 2 and 11A shows amino acid sequences encoded by mouse GDF-1 transcripts; variant mouse GDF-1 sequences are described on page 19, lines 17-29, and page 28, line 30, to page 29, line 27; Figure 4 shows *in vitro* translated GDF-1; Figure 9 shows recombinant GDF-1 protein produced in bacteria (i.e., unglycosylated); Example 6 describes purification of GDF-1 protein; and Figure 11B shows an amino acid sequence encoded by human GDF-1 transcripts.

Thus, the invention as presently claimed is fully supported by Appellant's original disclosure.

(6) Issues

A. Under 35 U.S.C. 112, first paragraph, was it proper for the Examiner to reject claims 4-7, 22, 24-25 and 30 as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention (i.e., the "written description" rejection)?

B. Under 35 U.S.C. 112, first paragraph, was it proper for the Examiner to reject claims 4-10 and 22-33 as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to this it pertains, or with which it is most nearly connected, to make and/or use the invention (i.e., the "enablement" rejection)?

Appellant submits the final rejections are improper for the reasons discussed below and respectfully request their reversal by the Board of Patent Appeals and Interferences (i.e., the "Board").

(7) Grouping of Claims

There are two separate grounds of rejection that apply to the pending claims. Thus, the claims of Group I (i.e., claims 4-7, 22, 24-25 and 30) do not necessarily stand or fall together with the claims of Group II (i.e., claims 8-10, 23, 26-29 and 31-33). Please note that the following grouping of claims assumes that no new grounds of rejections are entered.

If the Board reverses both the written description and enablement rejections, then the claims of both Group I and Group II would be allowable.

But if the Board reverses the written description rejection and affirms the enablement rejection, then no claims would be allowable.

In contrast, if the Board reverses the enablement rejection and affirms the written description rejection, then the claims of Group II would only stand as objected to because they depend from a rejected claim.

Of course, if the Board affirms both the written description and enablement rejections, then none of the claims would be allowable.

Therefore, Appellant submits that due to the arguments presented below, the Board should separately consider the patentability of the claims of Group I and Group II when deciding whether the Examiner's rejections are improper.

(8) Arguments

A. Appellant's Original Disclosure Provides a Written Description for the Invention Recognizable by the Ordinarily Skilled Artisan

"A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Univ. of Calif. v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Here, the specification describes by nucleotide sequence a mouse cDNA, variant mouse sequences, and a human cDNA. The examples of the specification show the isolation of a mouse GDF-1 gene and its use to isolate a human GDF-1 gene. The nucleotide sequences of both are used as non-limiting illustrations of the claimed invention, and are representative of the genus. But a hamster GDF-1 gene is also shown in Figure 5 by Southern blot analysis using cross-hybridizing mouse or human probes (page 9, lines 1-13) although a hamster cDNA clone was not sequenced; instead, the existence of the hamster GDF-1 gene was shown by cross-hybridization. Figure 14 shows that such cross-hybridization will detect a single-copy gene for GDF-1.

Furthermore, the ability to distinguish DNA segments the GDF-1 gene from mammalian genomic DNA is shown in the examples. Example 3 states, "Even at high stringency, the GDF-1 probe detected a single predominant band in both hamster and human DNA (see Figure 5), indicating that GDF-1 is highly conserved across species" (page 22, lines 25-29). Furthermore, Example 8 states, "As shown in Figure 14, both murine and human probes derived from the GDF-1 open reading frame hybridized to the same pattern of bands in human DNA, verifying that the human gene is indeed the homolog of murine GDF-1." (page 31, line 37, to page 32, line 4). Thus, the original disclosure clearly shows that specific hybridization with probes that contain the nucleotide sequences shown in Figure 2 or 11A or 11B uniquely identifies a single DNA segment.

Here, in contrast to *Univ. of Calif. v. Eli Lilly and Co.*, the chemical structures of mouse and human GDF-1 have been described and the existence of further genes is shown to be detectable by the property of cross-hybridization. Figure 14 shows that stringent hybridization uniquely identifies GDF-1 genes.

Finally, the ability to compare members of the TGF-β superfamily assists in the definition of GDF-1 genes and their cDNAs because they would be more related to each other at the level of amino acid sequence than to other members of the superfamily (cf. page 31, lines 18-22, to Figure 3B). Southern blot analysis does not detect other bands that would represent non-GDF-1 members of the superfamily (see Figure 14). Thus, other members of the claimed genus (e.g., a hamster cDNA) would have an amino acid sequence that is more related to the mouse and human GDF-1 sequences than other members of the TGF-β superfamily. A skilled artisan

could easily determine whether an amino acid sequence derived from a novel cDNA is GDF-1 or not by such structural features.

Thus, Appellant respectfully requests that the Examiner's written description rejection should be reversed by the Board.

B. The Specification Enables the Skilled Artisan to Use Appellant's Invention

A rejection based on an alleged lack of enablement requires that evidence, or a reason, be provided by the Examiner to substantiate an assertion that the objective truth contained in the disclosure is doubted. M.P.E.P. § 2164.01. This burden of persuasion has been described by the Office's reviewing court:

> "[I]t is incumbent on the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure."

In re Marzocchi, 169 USPQ 367, 370 (CCPA 1971).

The Examiner appears to maintain that enablement of Applicant's invention requires working examples showing one or more biological functions of GDF-1. See, for example, pages 2-3 of Paper No. 3. Appellant submits that this is not the proper standard for patentability under Section 112, first paragraph, because the biological function of a protein is only one potential use for his invention. For example, the specification clearly supports the use of GDF-1 as a lineage marker (i.e., "one potential use for GDF-1 as a diagnostic tool is as a specific marker for the presence of tumors arising from cell types that normally express GDF-1," page 12, lines 20-23) and the preparation of antibodies directed against GDF-1 (Example 5) that can be used to detect this marker. The Examiner does not cite a single statute, regulation, or case in support of her proposition that a gene is enabled only by a working example that demonstrates a biological function of the protein encoded by a gene. But without accepting this proposition as a proper statement of the enablement requirement under Section 112, first paragraph, Appellant has submitted evidence on April 24, 1999 in the form of the Ebendal Declaration that rebuts the Examiner's contention that the biological activity of GDF-1 could not be predicted (see page 2, lines 11-18, of Paper No. 3).

Below, Appellant shows the following: (i) the specification's prediction that GDF-1 can be used as a cell survival molecule in neuronal cultures has proven correct and (ii) the GDF-1 protein as illustrated by the amino acid sequences shown in Figures 2 and 11A-B can be used as a lineage marker.

(i) Use of GDF-1 as a Neuronal Cell Survival Molecule Enables the Invention

Appellant's specification states on page 14, lines 2-8, "If GDF-1 possesses [an activity similar to the nerve cell survival molecule activin], as is indicated by its specific expression in the central nervous system (see below), GDF-1 will likely prove useful *in vitro* for maintaining neuronal cultures for eventual transplantation or *in vivo* for rescuing neurons following axonal injury or in disease states leading to neuronal degeneration." Thus, one biological function of GDF-1 is described by the specification as its potential usefulness as a neuronal cell survival molecule. This function is not a statement of utility added after the filing of the application.

The Examiner reviewed the specification and stated on pages 2-3 of Paper No. 3, "Biological properties are alleged based upon the similarity of the GDF-1 amino acid sequence to the TGF-β family. However, there is no evidence of record that GDF-1 is a biologically useful protein possessing any particular properties. (See specification pages 10-11.) The similarities between GDF-1 and the TGF-β family members range from 26-52% on the amino acid level and these proteins are not deemed to be predictive of the biological properties possessed by GDF-1. The biological properties of the TGF-β family are diverse and it could not be predicted which activity GDF-1 would have, if any. As such, the specification does not enable using the GDF-1 protein as disclosed in the specification." Although Appellant did not agree with the Examiner that a biological property of GDF-1 could not be predicted and he maintains that the Examiner has not provided the objective evidence required under *In re Marzocchi* to contest the prediction that GDF-1 acted as a neuronal cell survival molecule, the Ebendal Declaration was submitted to rebut the Examiner's conclusion that GDF-1 activity could not be predicted.

The Ebendal Declaration was submitted on April 24, 1998 and shows that GDF-1 potentiates the effect of neurotrophin-3 (NT-3) protein on neuronal fibre outgrowth in an *in vitro* culture system. Thus, this evidence supports the predicted activity of GDF-1 as a cell survival molecule in *in vitro* culturing of neurons and rebuts the Examiner's allegation that it could not be so predicted. Appellant

stresses that the Ebendal Declaration was submitted only to rebut the Examiner's conclusion that GDF-1 activity could not be predicted as done in the specification. The Declaration does not represent an added statement to enable use of GDF-1 protein because, as should be understood by the Board, such post-filing statements would not be effective when it is the specification as originally filed that must teach the skilled artisan how to use the claimed invention. It is the specification's teaching that GDF-1 protein has a potential use as a neuronal cell survival molecule because of its expression in the brain that enables Appellant's claimed invention.

Appellant submits that use of GDF-1 as a neuronal cell survival molecule is both described in the specification and enables his claimed invention.

(ii) GDF-1 Proteins Are Enabled by Their Use as a Cell Lineage Marker

Appellant's specification states on page 12, lines 20-23, "one potential use for GDF-1 as a diagnostic tool is as a specific marker for the presence of tumors arising from cell types that normally express GDF-1." The specification also teaches what cell types normally express GDF-1 by illustrating its temporal- and tissue-specific expression in Example 4.

Thus, as taught in the specification, a GDF-1 probe can be used to determine whether a tumor arose from a cell of the surrounding tissue (i.e., a primary tumor) or was a metastasis from a different tissue. This use is not limited to detection of GDF-1 transcripts because the GDF-1 protein would also be expressed in a cell-specific manner. Example 5 describes (a) the use of recombinant GDF-1 protein to prepare antibodies directed against GDF-1 and (b) the use of such antibodies in Western blot analysis and immunoprecipitation.

Thus, as an alternative to detection of cell-specific GDF-1 transcription, the GDF-1 protein can be detected directly as a cell lineage marker for the origin of a tumor using an antibody prepared against recombinant GDF-1 immunogen. Appellant submit that use of GDF-1 protein is both described in the specification as "a specific marker for the presence of tumors" and it enables his claimed invention.

* * *

Finally, Appellant submits that the Examiner is being inconsistent in her contention that satisfying Section 112, first paragraph, requires conclusive proof of a gene's biological function. For example, U.S. Patent Nos. 6,008,017 and 6,074,841

contain claims of similar breadth to those on appeal and the specifications fail to provide evidence of the biological function of human cardiac/tolloid-like protein and Don-1 polypeptide, respectively. On the facts of record, there is no explanation why the Examiner has required that Appellant's specification provide working examples that show the biological function of GDF-1 when the specifications of these other patents do not provide such proof.

For the reasons discussed above, reversal of the Examiner's rejection is respectfully requested.

Appellant submits that the pending claims are in condition for allowance and earnestly request an early Notice to that effect. The Board is invited to contact the undersigned if further information is needed.

Respectfully submitted,

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4. A mammalian GDF-1 protein substantially free of proteins with which it is naturally non-covalently associated.

5. The protein according to claim 4 which is unglycosylated.

6. The protein according to claim 4 wherein said mammal is a mouse, hamster or human.

7. The protein according to claim 4 wherein said protein is chemically synthesized.

8. The protein according to claim 4 wherein said GDF-1 protein has a amino acid sequence as defined in Figure 11A or 11B.

9. A recombinantly produced GDF-1 protein having the GDF-1 amino acid sequence given in Figure 2, 11A or 11B.

10. The protein according to claim 9 wherein said protein is unglycosylated.

22. The protein according to claim 4 wherein said GDF-1 protein has a molecular weight of 41K or 38K as determined by SDS-PAGE.

23. The protein according to claim 9 wherein said GDF-1 protein has a molecular weight of 41K or 38K as determined by SDS-PAGE.

24. A process for purification of GDF-1 protein comprising expressing GDF-1 protein in a mammalian cell line, said GDF-1 protein being secreted into the medium, and isolating said GDF-1 protein from said medium to obtain a product which is substantially free of protein with which it is non-covalently associated.

25. The process according to claim 24 wherein said GDF-1 protein is unglycosylated.

26. The process according to claim 24 wherein said GDF-1 protein has a GDF-1 amino acid sequence as shown in Figure 2.

27. The process according to claim 24 wherein said GDF-1 protein has a GDF-1 amino acid sequence as shown in Figure 11A or 11B.

28. The process according to claim 24 wherein said GDF-1 protein is encoded by a human nucleotide sequence.

29. The process according to claim 24 wherein said GDF-1 protein is encoded by a mouse nucleotide sequence.

30. The process according to claim 24 wherein said GDF-1 protein has a molecular weight of 41K or 38K as determined by SDS-PAGE.

31. The protein according to claim 4 wherein said GDF-1 protein has a GDF-1 amino acid sequence as defined in Figure 2.

32. The protein according to claim 9 wherein said protein has the GDF-1 amino acid sequence given in Figure 2.

33. The protein according to claim 9 wherein said protein has the GDF-1 amino acid sequence given in Figure 11A or 11B.